REMARKS

Claims 14-38 have been canceled. Claims 1-13 were previously canceled. New Claims 39-54 have been added and are now active in this case.

SUPPORT FOR AMENDMENTS

New Claim 39 results from the combination of previous Claims 14 and 15. No new matter has been added, and no new limitations have been presented for consideration after final rejection.

REQUEST FOR RECONSIDERATION

The present invention provides a dry powder inhaler composition containing:

1. One or more particular active ingredients, and;
2. A roller dried anhydrous β-lactose having a mean particle size comprised between 50 and 250 μm.

The various aspects of terms within new independent Claim 39 are discussed below.

a) *Dry powder inhaler* (DPI) is a system designed for the inhalation and/or lung administration of dry powders. DPI's by definition do not contain liquids under any form (solvent, propellant, liquified gazes...). This is axiomatic by definition.

b) *One or more particulate active ingredients* are also called drugs. The drug or drugs are present in the solid (particulate) form. The drug is not in solution and/or in suspension. See a) above. The particle size for lung administration is generally comprised between about 0.5 and 10 μm.

c) *Roller-dried anhydrous β-lactose*. The β-anhydrous lactose is produced from a solution of lactose in water (in water the lactose is in the β-form) which is dried extremely rapidly (water is evaporated) using counter-clock rotating steam heated drums for instantaneous water removal. This fast removal is essential to avoid the transformation of the β-lactose into ∝-lactose. Also, β-lactose roller-dried has a rugosity comprised between 1.9 and 2.4.

d) *β-lactose carrier particle size of between 50 and 250μm.*

The consequence of the use of β-lactose with a particle size comprised between 50 and 250μm have been investigated with considerable detail, and the results thereof are described in the present specification of page 12, table 2 and are summarized further below.

Before proceeding, however, it is noted, in particular that the preamble term "dry powder inhaler pharmaceutical composition" is a claim limitation that must be given weight in the interpretation of all of claims 39-54. Under the standard of Loctite Corp. v. Ultraseal, Ltd., 228 U.S.P.Q. 90 (Fed. Cir. 1985), this preamble term "breathes life and meaning into the claims."

Claims 14-16 and 31 stand rejected under 35 U.S.C. §102(e) as being anticipated by Cutie et al. '905.

Cutie et al. '905 fails to either disclose or suggest the present invention.

Notably, Cutie et al.'905 disclose aerosol drug formulations consisting of a solution and/or a suspension and/or a combination of solution and suspension (slurry) of the drug in a liquid. The liquid may be a liquified gas known as propellant or any other liquid. In the case of a liquified gas, also known as propellant, the energy for the aerolization comes from the transformation of phase (liquid to gas) of the propellant. In case of another type of liquid, the aerolization energy may be supplied by mechanical means such as a pump incorporated or not into the metered valve or any other suitable aerolisation energy supply.

The drug may be dissolved or suspended in the propellant or in a combination slurry — solution (col. 1 line 28 - 31)

This type of lung drug dispensing system is known as a Metered Dose Inhaler (MDI) (col. 1 lines 43 - 44).

1.0 The Problem Addressed by Cutie et al. '905

- For many years, chlorofluorocarbons (CFC's) were used as liquified gas propellant for MDI'S. About a decade ago CFCs were found to damage the earth's ozone layer. Thus, it was recommended that they be phased out by the end of the twentieth century.

Recently, the U.S. Food and Drug Administration (FDA) decided to ban all CFCs by March 2008. (col 1,lines 45-54)

- Unfortunately, few propellant systems have been discovered which are suitable alternatives to CFCs in MDIs (col. 1 lines 54-56).
- Non-chlorinated propellants known as hydrofluorocarbon (HFC) are among the only possible alternatives. Unfortunately, this substitution (HFC for CFC) in MDIs is not straightforward. Some of the most important problems encountered during this substitution are lack of drug solubility, drug stability, delivery problems as well as drug particle size issue. (col 1, lines 57-65)
- Clearly, drug particle size is not a problem when the drug is dissolved into the propellant (liquid). Worse yet, the HFCs, in general, have a lower solubilization capability than the CFCs (col. 2 lines 15 - 17). With decreased drug solubility since the drug is not in a true solution, it may precipitate out, crystals may grow and/or crystals may agglomerate, all of which leads to an increase of drug particle size which will reduce dramatically the performance of such formulated MDIs.

2.0 The Solution Provided by Cutie et al. '905

2.1. PriorArt

Methods for controlling the particle size of the drug in MDIs (solution, suspension and/or slurry) are known and are:

- Adding one or more surfactants, which can improve solubility and the particle dispersability.
- Adding one or more co-solvents that can increase the solubility of the drug but can also trigger crystal formation caused by temperature variations.

2.2. The Discovery of Cutie et al. '905

Cutie discloses the use of micronized β-lactose as an aid for the incorporation, dispersion

and solubilization of drugs and excipients in solution/suspensions containing HFC-hydrocarbon or CFC propellants and/or a combination thereof (col. 3 lines 13 - 19).

More specifically, Cutie discloses (col. 3 lines 21 - 33), and all the independent claims 1, 18, 20, 21, 22, 24 and 25 recite, the following:

An aerosol formulation for mucosal or topical administration of a medicament which contains:

1. An effective amount of drug

2. A sugar, preferably lactose, most preferably β-lactose, with particle size below 10 and preferably below 2μm.

3. A propellant selected for the group of hydrocarbon, chlorofluorocarbons (CFC), hydrofluorocarbon (HFC) or a mixture thereof.

Cutie also provides a detailed description of the sugar:

(Col. 3 lines 62 - 64) the sugar is acting as a solid diluent/dispersant to aid in the incorporation of the dispersion of or solubilization of actives and excipients in the propellants.

(Col. 4 lines 15 - 24) the sugar is capable of:

(1) Facilitating the dispersion of the drug and/or excipient.

(2) Stabilizing formulations physically and/or chemically.

(3) Facilitating the transport of the aerolized drug.

(4) Facilitating the drug micronization.

(5) Acting as a respiratory sensitizer or desensitizer of drug surface interaction at topical and/or mucosal surfaces.

(6) Acting as a density modifier (of the solution /suspension)

(Col. 4 lines 56 - 61 the concentration of the sugar should be approximately 1/100 to 1/10 that of the drug.

(Col. 4 line 62 - 67 and col. 5 lines 1-4.

- The particle size of the sugar should be no greater than 10μm since larger particles are not transported to the airways effectively.
- The preferred sugar particle size is less than 2μm.
- There is no lower limit as sugar particle size.
- Particles less than 0.5μm tend to be exhaled by the patient.

While Cutie states clearly that the largest "sugar" particle size shall be 10μm, it is clear that while larger particles will render the "solibilizing" and/or "densifying" effect less effective they also will have an adverse effect on the suspension since the larger the sugar particles the easier they will precipitate out from the solution/suspension. Also, larger particles will have the negative effect of clogging the metering valve rendering the MDI system unusable.

Cutie discloses a new type of aid to maintain the drug in solution/suspension and inhibit crystal growth called a solubilizer/suspension aid. These substances may be any sugar with a particle size less than 1μm, which is added to the mixture propellant (liquid) and micronized drug. Sugars such as lactose, manitol, sorbitol fructose galactose, n-lactose are suitable for use.

The reason for addition of these sugars is to:

- Aid in the incorporation, dispersion and solibilization of drug and excipients in the liquified gas (propellant).
- Facilitate the dispersion drug and/or excipient.
- Stabilize the formulation.
- Facilitate the transport of aerolized drug.
- Facilitate the micronization.
- Act as a repiratory sensitizer or desensitizer of drug substance.
- Act as a density modifier interaction at topical and/or micronized surface.
- Maintain a sugar concentration at about 1/100 to 1/10 of the drug.

3.0 The present invention is quite different from that of Cutie.

First, the teachings of Cutie (use of micronized β-lactose) are of no use for the present invention because:

1) The compositions of the present invention (dry powder mixtures) are not solutions/suspensions nor are they slurries; therefore, there is no need for a solubilization/suspension aid nor a densifier as in Cutie.

2) The addition of micronized β-lactose (in the range of single digit μm particle size) to the compositions of the present invention is of no use since it will negatively effect the pulmonary fraction. The particle size of the β-lactose carrier of the present invention is comprised between 50 and 250 μm, and which is clearly not micronized.

3) The use of β-lactose cannot facilitate the micronization since, in the present invention, the drugs (active ingredients) are not micronized with the β-lactose.

4) Since the β-lactose carrier of the present invention has a particle size comprised between 50 and 250 μm, it cannot and will not reach the lungs when inhaled and therefore it cannot act as a respiratory sensitizer or desensitizer.

5) The β-lactose concentrations (lactose/drug) in the present invention are comprised between about 1 and 20,000, while the concentration disclosed by Cutie is comprised between 0.1 and 0.01.

6) The superiority of the β-lactose versus ∝-lactose has been clearly (and surprisingly) demonstrated in the present specification while Cutie teaches the use of sugars such as lactose, manitol, fructose, galactose. Thus, Cutie neither discloses nor suggests the observed superiority of the present β-lactose for DPI pharmaceutical compositions.

7) Further, to point 6), the present invention discloses β-lactose particles useful as a carrier in DPI compositions while Cutie teaches the use of micronized sugars (including β-lactose) as an aid for suspensions/solutions and or slurries in MDI compositions.

Clearly, one skilled in the art would not have been put in possession of the present invention by Cutie. For example, how could one skilled in the art utilize Cutie, relating to the use of micronized β-lactose as an aid in dispersing and solubilizing drugs in solutions/suspensions, to obtain the present invention which entails the use of particulate roller-dried anhydrous β-lactose excipient having a particle size comprised between 50 and 250 μm for a dry powder inhaler composition? Also, how could Cutie even suggest the present invention when the particle sizes taught by this reference (less than 10 μm) are much smaller than those required by the present invention? In fact, Cutie, with single digit μm particle sizes of micronized β-lactose, teaches away from the present invention.

In view of all of the above, this reference would neither have disclosed nor suggested the present invention to one skilled in the art at the time the present invention was made.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 14-38 stand rejected under 35 U.S.C. §103(a) in view of Cutie et al. '905, Sarlikiotis et al. '287, Ganderton et al. '386 and Tomkiewicz et al.

However, none of these references, either alone or in combination, would have either disclosed or suggested the present invention to one skilled in the art at the time the present invention was made.

Notably, the comments set forth above with respect to Cutie et al. '905 are deemed applicable to this ground of rejection as well and are incorporated herein.

U.S. Patent 6,284,287 (Sarlikiotis) teaches compositions for inhalation containing a micronized active ingredient with a mean particle size of 0.1μm to 10μm and a pharmaceutically acceptable excipient having a mean particle size of 200 to 1,600μm and a rugosity greater than 1.75.

Clearly, Sarlikiotis discloses any physiological acceptable excipient or excipient mixture (claim 1).

A list of proposed excipients acceptable, in accordance with the "287" patent, are listed at Col. 4, lines 8 - 18 and are:

- Inorganic salts such as sodium chloride, calcium carbonate.
- Organic salts such as sodium lactate.
- Organic components such as, for example, urea.
- Monosaccharides such as, for example, glucose and its derivatives such as, sorbitol, polyalcohols, mannitol, xylitols.
- Disaccharides such as, for example, lactose, maltose and their derivatives.
- Polysaccharides, such as, for example starch and its derivatives.
- Oligosaccharides such as, for example, cyclodextrins and also dextrins can be employed.
- Mixtures of the auxiliaries can also be employed.

Clearly, any excipient included in this very extensive list is acceptable for the purpose of Sarlikiotis which, as defined by claim 1, is a "formulation"? As a matter of fact Sarlikiotis is only preoccupied by the redispersion properties of the composition "co-agglomerates" (experiment 1) and by the "readily flowable" properties of all of the 7 composition examples.

Also in the examples, Sarlikiotis, uses as an excipient "commercially available lactose" and "commercially available sodium chloride." From this, one concludes without any doubt that Sarlikiotis teaches the use of any excipient included in its "extensive shopping list" and also that any excipient will produce the same result, i.e., a "readily flowable" composition.

Notably, despite the extensiveness of this list, β-lactose is not included.

Following the teachings of Sarlikiotis, one skilled in the art would expect all excipients listed in this list to be equivalent. Therefore, it is clear that Sarlikiotis does not and cannot teach the surprisingly advantageous use of any one specific excipient, and notably not roller-dried anhydrous β-lactose carrier particles with a particle size comprised between 50 and 250. The present specification clearly demonstrates the advantage of using said anhydrous β-lactose over all other kinds of lactose particles in terms of lung deposition of the active ingredient. The "287" patent is completely silent about this discovery. Notably, this patent teaches:

> A formulation consisting of readily flowable core agglomerates which have an improved redispersion at 60 and 30L/min flow are totally different from the present invention which is the "discovery of one or more excipients for the purpose of obtaining a high pulmonary fraction percentage as measured by the Twin impinger and the Anderson cascade impactor.

Since the purposes are different, it is not surprising that the results are different:

	Sarlikiotis	**Present Invention**
Excipient	Any	β-lactose (lactose roller-dried)
Particle Size B	400 - 1000μm	50 - 250μm
Rugosity	Greater than 1.7	1.9 - 2.4
Outcome	Flowability	High pulmonary fraction [%]
	Redispersion	

From the above tabular summary, it is clear that the teachings of Sarlikiotis would be of no use in obtaining the present invention since the purpose (flowability and redispersion versus high pulmonary fraction) and therefore, the outcome of each inventions, is totally different from the other (any excipient versus only β-lactose with a very narrow particle size).

U.S. Patent 5,376,386 (Ganderton et al.)

This patent discloses a crystalline particulate carrier useful in DPI which is selected from the group of monosaccharides, disaccharides and polysaccharides having an average particle size of from 5 to 1000μm, and wherein the particles have a rugosity of less than 1.75. Ganderton discloses carriers that:

> may be a crystalline non-toxic material which is acceptable for use in pharmaceutical compositions which does not destabilise the pharmaceutical active material with which it is formulated and which can be produced in a form having a rugosity of less than 1.75 [Emphasis added] (Col. 1, lines 62-67).

Col. 2 lines 5 - 11 gives a list of preferred carriers which are:

- Monosacharides such as fructose, manitol, arabinose, xylitol and dextrose (glucose) and their monohydrates.
- Dissaccharides such as lactose, maltose or sucrose.
- Polysaccharides such as starches, dextrins or dextroses.

From this list it is obvious that any saccharide may be used as long as it is crystalline and has a rugosity of less than 1.75.

Ganderton also recognizes that conventional excipients have a rugosity of at least 1.96 and generally greater than 2.0 (col. 1 lines 60 - 62). Therefore, the carrier particles useful for the "386" patent (with rugosity less than 1.75) have to be prepared by a very well controlled recrystallization process (col. 2 liens 24 - 36).

For example, to prepare crystalline lactose with a rugosity of less than 1.75, n- hexane and acetone are added to an agitated water solution of lactose which after crystallization is separated by filtration (col. 2 lines 66 to col. 3 lines 17). A more detailed preparation of the lactose useful for the Ganderton patent is given in example 1 and the so-prepared lactose is used in all other examples 1 to 7.

The importance of a rugosity of less than 1,75 for the "386" patent is well illustrated by the results obtained with the product of example 1 (table 1) and the product of example 6 and 7 summarized hereafter from Ganderton:

Influence of the nature of the lactose on the amount of drug, in percent of total dose, recovered at stage 3-7 (<5.5μm) of the Anderson Cascade Impactor or at stage 2 of the apparatus A of the British Pharmacopoeia 1988. Note: The higher the values the better the carrier.			
Lactose Type Origin	Regular Lactose Commercial Crystalline	Recrytalised Lactose Recrytalised as per "386" Example 1	Difference in [%]
Example 1			
At 60L/min flow	19.6	42.0	118
At 150L/min flow	5.4	22.0	307
Example 6	18.6 - 18.8	24.7 - 26.5	33-41
Example 7	14.4	24.9	78

From these examples it is clear that the lactose recrystallized in accord with Ganderton, yields a much higher amount of drug in the size range of under 6μm.

The important difference between these two lactoses is the **rugosity**, and clearly Ganderton teaches the use of a carrier with a rugosity not greater than 1.75 as well as a method for the manufacture of such carrier.

These teachings would be of no use in attaining the present invention since:

1. The rugosity of the β-lactose useful for the present invention is comprised between 1.9 and 2.4. (Ganderton teaches less than 1.7)
2. β-lactose can not be obtained by crystallization because as soon as lactose crystallizes it becomes α-lactose.

In solution (water), lactose exists in the β-form, whereupon crystallization transforms into ∝-lactose. To obtain β-lactose, the water containing the n-lactose has to be evaporated extremely fast so as to avoid (not allowing time for) the transformation of β to α. This extremely fast water evaporation is possible by roller-drying the β-lactose solutions.

Moreover, Ganderton did not list β-1actose in the list of carriers because it is known that β-lactose cannot be obtained by crystallisation. Therefore, the rugosity cannot be controlled and reduced to less than 1.75.

This patent thus teaches away from the use of β-lactose as a carrier since the rugosity is much greater than 1.75 and the rugosity cannot be adjusted by recrystallisation.

Tomkiewicz et al. (1994) describes the mucolytic activity of N-acetylcysteine-L-lysinate (NAL) when administered to dogs using an Metered Dose Inhaler (MDI). This is a Pharmacodynamic study of the effect of NAL on the dog mucus rheological properties and it does not address DPI compositions of NAL. Thus, it is irrelevant to one skilled in the art attempting to attain the present invention.

Hence, even the combined teachings of these references would fail to put one skilled in the art in possession of the present invention.

Notably, in addition to the deficiencies of Cutie et al., Savlikiotis may use any excipient as long as it improves flowability and dispersion. None of the cited references relates to improving "pulmonary fraction (%)."

Ganderton teaches the use of any crystalline carrier having a rugosity of less than 1.75, which teaches away from the present invention.

Finally, Tomkiewicz et al. pertains to a MDI and to a DPI composition as in the present invention.

Clearly, and in fact, the combined teachings of these references would either be incompatible or would teach away from the present invention.

However, even assuming, arguendo, that the present invention would have been obvious to one skilled in the art in view of the cited references, attention is directed to the following table from

page 12 of the present specification which evidences the unexpectedly superior pulmonary fraction (%) obtained when using β-lactose as compared to ∝-lactose in the claimed particle size ranges.

Specifically, the following table shows the influence of the nature and particle size of lactose carrier on the in vitro pulmonary fraction, expressed as percent of total dose, of NAL (active ingredient) measured by using the twin impinger at 60 L/min.

NOTE: The higher the values the better the carrier.

	∝-lactose			β-lactose		
Particle Size [μm]	**63 - 100**	**96 - 125**	**100 - 160**	**63 - 100**	**96-125**	**100 - 160**
Pulmonary Fraction [%]	28	28	28	35	39	42

The pulmonary fractions are 28% for ∝-lactose versus 35 to 42% for β-lactose with an increase of 25 % to 50 % for the latter over the former.

This demonstrates, surprisingly the superiority of β-lactose versus ∝-lactose as a carrier for the claimed particle size range for DPI inhalation compositions. Clearly, one skilled in the art would have no reason to expect this result in view of the art of record.

Thus, in view of all of the above comments, and the comparative data shown above in the Table - which data is already of record in the present specification, it is clear that the present invention is patentable over the art of record.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Accordingly, it is believed that this application is now in condition for allowance. Early notice to this effect is earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 07-1337 and please credit any excess fees to such deposit account.

Respectfully submitted,

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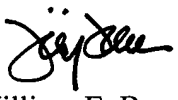

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